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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/295,663	04/21/1999	PHALGUN B. JOSHI	16303-007120	7445

7590 10/22/2002

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EXAMINER
WOITACH, JOSEPH T

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 10/22/2002 24

Please find below and/or attached an Office communication concerning this application or proceeding.

File

Office Action Summary	Application No. 09/295,663	Applicant(s) Joshi et al.
	Examiner Joseph T. Woitach	Art Unit 1632

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *Aug 5, 2002*

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *38-44, 47-54, and 69-87* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideratio

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *38-44, 47-54, and 69-87* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examine

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some* c)☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Request for Continued Examination

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on August 5, 2002, paper number 22, has been entered.

DETAILED ACTION

This application, filed April 21, 1999, claims benefit to provisional applications: 60/082,665 filed April 22, 1998, 60/111,635 filed December 9, 1998, and 60/11,637 filed December 9, 1998.

Applicants' amendment filed August 5, 2002, paper number 23, has been received and entered. Claim 46 has been canceled. Claims 38, 41-44, 49-54, 69 and 71-74 have been amended. Claims 85-87 have been added. Claims 38-44, 47-54 and 69-87 are pending and currently under examination.

Drawings

This application has been filed with informal drawings which are acceptable for examination purposes only. Formal drawings will be required when the application is allowed.

Further, it is noted that figure 16 has been amended with handwritten comments however, the amendment has not been initialed nor is it clear from the figure legend to what the amendment refers.

Claim Objections

Claim 42 is objected to because of the following informalities: "GDEPT" is the acronym which is not specifically defined in the specification or the art of record. When not specifically defined in the specification, the first presentation of an abbreviated term should be denoted by setting forth the full name indicating the term to be used subsequently.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 38-44, 47-54, 69-77 and 78-84 previously rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for inhibiting growth of cancer cells in a subject wherein vincristine sulfate and cisplatin and a polynucleotide encoding a gene known to inhibit cell growth, does not reasonably provide enablement for enhancing the therapeutic effect of a foreign gene in a subject is withdrawn.

Initially, it is noted that claims 38-44, 47-54 have been amended to encompass the delivery of "a nucleic acid encoding a foreign gene" "wherein the transfection efficiency is increased by at least 50%", and do not require an increased therapeutic effect. Further, the methods of treatment of cancer encompassed by claims 69-77 requires that the method result in "a transfection efficiency [which] is increased by at least 50%". Applicants argue the claims 38-44, 47-54 are directed to method of delivery and do not require any therapeutic effect, and could be used to increase the delivery efficiency of any polynucleotide, and therefore should not be subject to or limited to providing a therapeutic effect. Additionally, with respect to claims 69-77, Applicants point out that the method steps themselves can easily be performed. Further, given that several working examples are provided in the present specification and shown to be effective in reducing tumor cell growth, Applicants argue that the present method as presently claimed would not require undue experimentation to practice. Applicants' arguments have been fully considered and found persuasive. Therefore, in light of the claim amendments and upon consideration of Applicants' arguments, the rejection is withdrawn.

Claims 38-44, 47, 48 and 69-87 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a methods of introducing a nucleic acid encoding a foreign gene and of inhibiting the growth of cancer cells comprising the steps of: (a) first, administering a cell cycle blocking agent; and (b) second, administering a nucleic acid wherein the transfection efficiency is increased by at least 50%, does not reasonably provide enablement

for administering the nucleic acid before the cell cycle blocking agent wherein the transfection efficiency is increased by at least 50%. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

The present claims are drawn generally to a method of delivering a polynucleotide to a patient wherein practicing the method results in a 50% increase in transfection efficiency. The

methods encompass essentially two steps (a) the administration of a the cell cycle blocking agent and (b) the administration of a polynucleotide. Though the claims recite steps (a) and (b), the claims encompass administering a cell cycle blocking agent and administering a polynucleotide wherein the administration of either the cell cycle blocking agent and the polynucleotide can be performed in any order. As set forth in dependent claims 48-54, the claims clearly set forth conditions wherein one step of administration is performed before the other. The basis of the instant rejection focuses on the order in which the method steps are performed, specifically the requirement to administer the cell cycle blocking agent prior to the administration of the polynucleotide to achieve the transfection efficiency encompassed by the claims. It is noted that dependent claims 49-51 set forth that the administration of the cell cycle blocking agent is prior to the administration of the polynucleotide, and therefore, is not subject to the instant rejection.

The present invention is based on the observation that cell cycle synchronization of the target cells in a subject results in an increased efficiency of transformation *in vivo* (see specification pages 3-4, and first line in Summary of the Invention, page 4). The working examples provided in the present disclosure demonstrate that the prior administration of a cell cycle blocking agent increases the efficiency of cell transformation. The affect of the cell cycle blocking agent is not immediate and requires several hours for the cells to become synchronized (see for example figures 1, 2, 5(c) and 9). Importantly, the affect of the cell cycle blocker on transfection efficiency is transient and changes and decreases over time (see for example figures 10-12). The specific effect of the cell cycle blockers on the cells and their ability to increase the

efficiency of transfection is unknown. A review of the working examples indicates that each of the cell cycle blockers has different effects on the transfection efficiency, indicating that process of determining the ability of a particular compound to increase efficiency is empirical. This observation is supported by Son *et al.* who evaluate several chemotherapeutics (see figure 4) (known to be cell cycle blockers by virtue of their DNA damaging effects) and find only ciplatinin to have a significant effect on DNA/liposome delivery to a tumor cell (summarized in discussion on page 12672). Further, Son *et al.* propose that the affect may also vary among different tumors and cell types, and does not correlate to a cells sensitivity or resistance to a given compound (top of page 12672). Further, the composition used to deliver the polynucleotide can dramatically affect the efficiency. For example, figure 4 demonstrates that a liposomal composition can dramatically decrease the efficiency over no liposome when administered with methotrexate or doxorubicin (see figure 4). The effectiveness of a cell cycle blocker to increase transfection efficiency is empirical in nature and the various parameters one must test such as the route of delivery, the times of delivery, the concentration of the cell cycle blocker, the concentration of nucleic acid, and the testing of various agents such as a liposomes on the ability of the cell blocker to function, without a reasonable expectation of succeeding in an increasing the efficiency would constitute undue experimentation. The numerous working examples provide a starting point for the optimization and practice of a method for the delivery of the cell cycle blocker before the delivery of the nucleic acid, however they fail to provide the

necessary guidance for the delivery of a cell cycle blocking agent following the delivery of the nucleic acid.

In view of the lack of guidance, working examples, breadth of the claims, the level of skill in the art and state of the art at the time of the claimed invention was made, it would have required undue experimentation to make and/or use the invention as claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 38-44, 47-52, 69-73, 79-81 and 84-86 are rejected under 35 U.S.C. 102(b) as being anticipated by Son *et al.*

Applicants summarize the requirements for anticipation under 35 USC 102 and argue that the present claims as amended are not anticipated by Son *et al.* In particular, Applicants note the transfection efficiency must be increased by at least 50%, and note that the results of Son et al. only demonstrate a 30% increase in efficiency. See Applicants' amendment, pages 8-9. Applicants' arguments have been fully considered, but not found persuasive.

Examiner notes the claim amendments, and the requirement of the instantly claimed method to increase transfection efficiency at least 50%, however the results presented in Son *et al.* meet this limitation. Applicants indicate that the results present in Son *et al.* demonstrate an increase of 30%, however the 30% presented in results represents a measured CAT activity as a percent conversion. Each of the percent activities should be interpreted as a factor of the control showing little or no activity. For example in figure 2, the 30% activity at day 7 represents approximately 300 fold increase over the control. Likewise, the pretreatment of the cells in culture (figure 3) and the analysis of the affects of various chemotherapeutic agents (figure 4) must be interpreted with respect to the control, not as an absolute value. This interpretation is consistent with Son et al. who interpret the affects of pretreatment as having "about a 2-fold more transfectability" than other samples (page 12671, top of second column describing figure 3). A two-fold increase would be a 200% increase in transfection efficiency. Thus, the methods and conditions set forth in Son *et al.* meet the limitations of the present claims. Therefore, for the reasons above and of record, the rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made

to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 38-44, 47-54, 69-73, 79-81 and 83-86 are rejected under 35 U.S.C. 103(a) as being unpatentable over Roth *et al.* and Son *et al.*

Applicants note the amendments to the claims, and point out that the teaching of Son et al. no longer anticipates the embodiment of increasing efficiency at least 50%. Moreover, Applicants note that Son et al. try several anticancer agents, and besides cisplatinin none had any significant affect on transfection efficiency. The teaching of Roth *et al.* fail to remedy the deficiencies of Son *et al.*, and provide no motivation to use the agents disclosed in Roth *et al.* See Applicants' amendment, pages 9-11. Applicants' arguments have been fully considered, but not found persuasive.

As noted above in the response to arguments presented in the 35 USC 102 rejection, the results presented in Son *et al.* do meet the limitation of increasing the transfection efficiency at least 50%. With respect to the other agents besides cisplatinin, Examiner would agree that the efficiencies are not as dramatic, however a close analysis of the results presented in figure 4 indicate an increase in transfection efficiency for all of the compounds over control. Each of the

measured activities must be interpreted and extrapolated to percent efficiencies or from one sample composition to another. In the instant case, though each of the compounds tested does not demonstrate as great as increase as cisplatinin, each demonstrates a significant increase over the control, thus represents an increase greater than 50%. Thus, the methods and conditions set forth in Son *et al.* and Roth *et al.* meet the limitations encompassed by the present claims, and the combined teachings make obvious the instantly claimed methods. Therefore, for the reasons above and of record, the rejection is maintained.

Claims 38-44, 47-54, 69-73 and 78-86 are rejected under 35 U.S.C. 103(a) as being unpatentable over Roth *et al.*, Son *et al.* and Walker *et al.*

Applicants summarize arguments over Roth *et al.* and Son *et al.* and summarize the teaching of Walker *et al.* as a method for the delivery of a liposome composition and contains no mention for the use of the methodology in conjunction with a cell cycle blocker. See Applicants' amendment, pages 11-12. Applicants' arguments have been fully considered, but not found persuasive.

The teaching of Walker *et al.* was provided to demonstrate that various methods for the delivery of liposomal compositions were known and practiced in the art. Examiner would agree that there was no specific motivation in Walker *et al.* to combine the methodology with a cell cycle blocker, however the methods of Walker et al. are general methods providing an improvement for the delivery of liposomal compositions. The successful results presented in

Son *et al.* for the effectiveness of certain liposomal compositions provides motivation to use any delivery method conventional in the art. In particular the methods taught by Walker *et al.* provide an improvement for the increased efficiency of delivery of liposome compositions. The specific motivation of Son *et al.* to use their observation in gene therapy protocols provides adequate motivation to optimize known delivery protocols in maximizing the delivery of a given polynucleotide. Given the teachings and successful results of Roth *et al.* and Son *et al.* for the potential treatments of cancer cells, one would have been motivated to use the teachings of Walker *et al.* for delivery protocols who also discusses use of the delivery protocols as noted by Applicants for the killing of cells. Therefore, for the reasons above and of record, the rejection is maintained.

Claims 74-77 and 87 are rejected under 35 U.S.C. 103(a) as being unpatentable over Roth *et al.*, Son *et al.* and Bally *et al.*

Applicants argue that combined the teachings of Roth *et al.* and Son *et al.* fail to meet the limitations of the present claims, and that Bally *et al.* fails to remedy the deficiencies. It is noted that Bally *et al.* dose not disclose the use of any cell cycle blocking agent and provides no motivation to combine the teachings with Roth *et al.* and Son *et al.* See Applicants' amendment, pages 12-13. Applicants' arguments have been fully considered, but not found persuasive.

As reasons with the teaching of Walker *et al.*, the teachings of Bally *et al.* was provided to demonstrate methods which were known and practiced in the art for the delivery of a

polynucleotide. Examiner would agree that there was no specific motivation in Bally *et al.* to combine the methodology with a cell cycle blocker, however the methods of Bally *et al.* are general methods providing an improvement for the gene delivery methods. The successful results presented in Son *et al.* for the effectiveness of certain compositions provides motivation to use any delivery method conventional in the art. In particular the methods taught by Bally *et al.* provide an improvement for the increased efficiency of gene delivery. The specific motivation of Son *et al.* to use their observation in gene therapy protocols provides adequate motivation to optimize known delivery protocols in maximizing the delivery of a given polynucleotide. In light of the teachings and successful results of Roth *et al.* and Son *et al.* for the potential treatments of cancer cells, one would have been motivated to use the teachings of Bally *et al.* for improved delivery protocols. Therefore, for the reasons above and of record, the rejection is maintained.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach whose telephone number is (703)305-3732.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached at (703)305-4051.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist Pauline Farrier whose telephone number is (703)305-3550.

Papers related to this application may be submitted by facsimile transmission. Papers should be faxed via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center numbers are (703)308-4242 and (703)305-3014.

Joseph T. Woitach

Deborah Crouch

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